Gout Pharmacology

Introduction

Gout is caused by hyperuricemia, and hyperuricemia is usually the product of underexcretion, genetically predetermined. Gout flares are caused by acutely increasing urate levels, precipitating crystals into joints, resulting in an inflammatory reaction. At this stage of your training, it is easiest to separate the management of gout into **acute treatment of inflammation** and **chronic treatment of urate levels**. Table 2.1 shows how you should think about gout pharmacology. Table 2.2 (toward the end) shows a similar but more complicated table used in the clinical sciences.

ANTI-INFLAMMATORY/ACUTE		URATE-LOWERING/CHRONIC	
Anti-microtubule	Colchicine	Xanthine oxidase inhibitors	Allopurinol, febuxostat
NSAIDs	Naproxen Ibuprofen	Uricosuric agents	Probenecid
Glucocorticoids	Intra-articular dexamethasone Oral burst prednisone	Uricase agents	Pegloticase Rasburicase

Table 2.1: Preclinical Perspective of Gout Pharmacology
A reorganization of gout medications with an emphasis on mechanisms.

Uric acid is produced by the metabolism of purine nucleic acids, and is excreted by the kidney. Chronic gout, or chronic hyperuricemia (the condition that puts the patient at risk for a gout attack), is managed by reducing the levels of uric acid in the blood chronically. Chronic gout treatment targets reducing uric acid levels. Acute gout flares are caused uric acid crystals precipitating into joints and being attacked by the immune system. While that precipitation of crystal likely occurs because of excess uric acid levels, an acute attack is treated with anti-inflammatories and not with the reduction of uric acid levels. We will first explore the treatment of acute gout flares, then consider the pharmacology involved in uric acid formation, and conclude with the pharmacology of uric acid excretion. Figure 2.1 is the summary of the entire lesson.

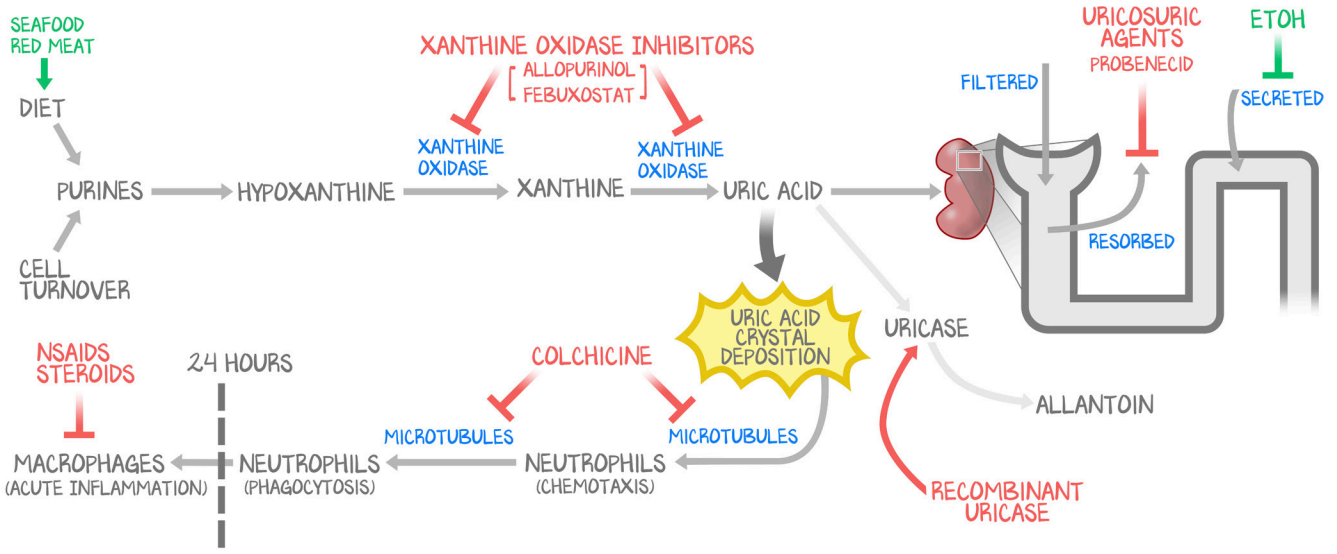

Figure 2.1: Summary Slide
Red meat and seafood can be eliminated from the diet to prevent accumulation of uric acid. Alcohol can be eliminated from the diet to disinhibit tubular secretion of uric acid. Carefully selecting diuretics and prophylactic aspirin based on comorbidities remains a balance between chronic disease management and provoking acute gout flares. For acute gout flares, anti-inflammatories are used: colchicine, NSAIDs, or steroids. To reduce the amount of uric acid created, xanthine oxidase inhibitors are used. As a last-ditch effort, uricosuric and uricase agents can be added.

Pathogenesis and Management of an Acute Gout Flare

When uric acid levels are high, urate crystals precipitate out of the serum and deposit into the joints. There, the cells of the synovium consume those uric acid crystals. They recognize these as foreign, and release proinflammatory cytokines to attract the innate immune system, the phagocytes. Neutrophils are the first cells to respond to invasion by a pathogen and are the predominant cell of inflammation for the first 24 hours. They establish the immune response to the flare. It doesn't matter whether the "invader" is a crystal or a living organism. The inflammation is equally real. During the first day, the flare is being established. "Inflammation" results in arterial vasodilation and venous pooling, both resulting in the calor, dolor, and rubor of inflammation. Pooling permits circulating macrophages to slow down in the bloodstream, grab onto the endothelial wall, and wiggle their way into the tissue that has the inflammatory signal. In the tissue, these phagocytes also wiggle their way to the source of "invasion." Once there, they do what they do—phagocytosis and release of inflammatory mediators. What makes matters worse is that the neutrophils that eat the uric acid crystals may regurgitate, releasing hydrolytic enzymes into the joint, causing further damage. After the first 24 hours, macrophages take over for neutrophils and the flare is well established. We just described "Acute Inflammation" from Inflammation and Neoplasia #4: *Wound Healing*. In gout, what matters is the timing.

That "wiggling" is **neutrophil margination** and **chemotaxis**. Both require the use of **microtubules**. Neutrophils are phagocytes that phagocytose the crystal. Phagocytosis relies on vesicle transport to move the phagosome to the lysosome to degrade what's inside. Vesicle transport requires **microtubules**. Since neutrophils are predominantly the cell of inflammation for the first 24 hours, any therapy target that targets neutrophils would be most effective early in the course of an acute gouty flare, within the first 24 hours of onset. If neutrophils don't establish the inflammation, they don't call for macrophage backup, the flare will not progress. **Colchicine** is a **microtubule formation inhibitor**, thereby inhibiting chemotaxis and vesicle transport of neutrophils. It is best used early in the course of the gouty attack and less effective after the first 24 hours. Colchicine is dose-limited by **diarrhea**. The diarrhea is because it also works on the microtubules of spindle formation of mitosis, making highly mitotic cells vulnerable to injury (such as enterocytes).

Once the gouty flare is well underway, colchicine doesn't work so well. Instead, we turn to general anti-inflammatory medications. **NSAIDs**, **intra-articular glucocorticoid injection**, or **oral glucocorticoid burst** are options. NSAIDs should be avoided in kidney disease. Oral glucocorticoids have worse systemic side effects and should be avoided in diabetics. Intra-articular glucocorticoids require a trained medical profession to administer. To reduce systemic symptoms, oral burst glucocorticoids and rapid-acting NSAIDs are equivalent in efficacy. You will not be asked to choose between them.

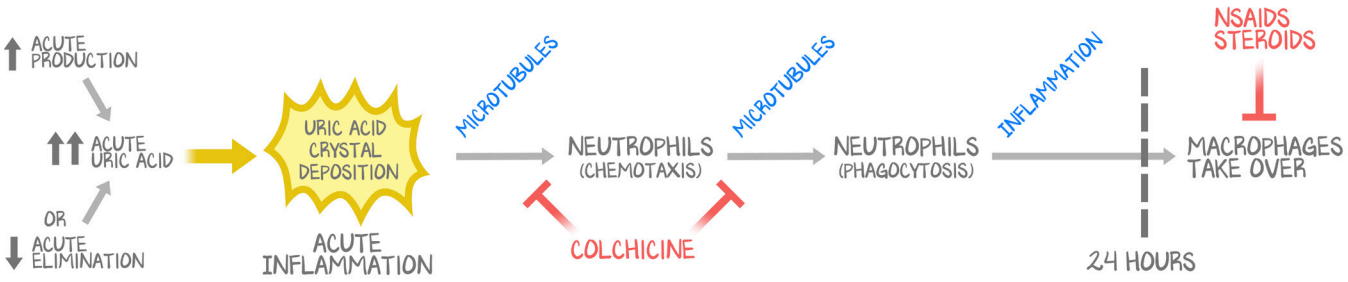

Figure 2.2: Acute Gout Flare Management Is About Inflammation, Not Uric Acid
Once in a flare, lowering uric acid levels won't help. Instead, because the acute flare is dependent on inflammation, anti-inflammatories are the focus. Colchicine is best used in the first 24 hours to prevent acute inflammation from being established. NSAIDs and glucocorticoids can be used at any time.

Pathogenesis and Management of Uric Acid Production

Uric acid comes from the metabolism of purines. Purines come from the metabolism of our own nucleic acids or from the food we eat. Purines are converted into uric acid by the enzyme **xanthine oxidase**.

To reduce uric acid synthesis, we could reduce purine metabolism. However, within each human, the rate of purine metabolism is mostly fixed; the amount of uric acid made is in equilibrium with uric acid excretion. The addition of extra purines to that equilibrium shifts the balance toward production and provokes an acute flare. Therefore, to reduce the chances of a flare, patients should **avoid seafood and red meat**, foods rich in purines.

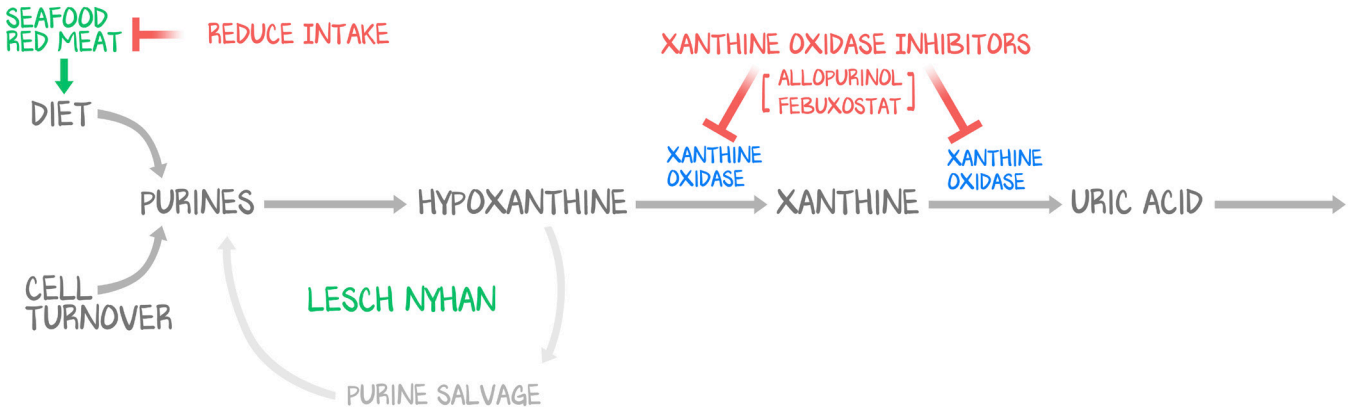

Figure 2.3: Figure 2.3: Lowering Uric Acid by Targeting Production
Diets rich in purines (seafood, red meat) increase the risk of developing hyperuricemia and therefore can precipitate a gout flare. Avoiding these triggers can help reduce flares. Inhibition of xanthine oxidase (allopurinol, febuxostat) limits uric acid levels and prevents precipitation of gout flares. There is no need to memorize this pathway; it is used only to illustrate the xanthine oxidase inhibitor mechanism of action.

To reduce uric acid synthesis, we can also use pharmacology. Inhibiting the formation of uric acid would thus tip the balance of equilibrium in favor of uric acid elimination. Pharmacologic urate-lowering therapy is chosen for those patients with an elevated uric acid level, tophi, radiographic evidence of chronic gout, or recurrent uric acid stones. If a patient has just one attack per year and has a mildly elevated uric acid, you don't need to treat. If someone has more attacks than that, or any evidence of joint damage, with an elevated uric acid, we try to get their uric acid levels down. **Xanthine oxidase inhibitors** reduce the amount of uric acid produced from the purines our body sees. The two you should know are **allopurinol** and **febuxostat**.

There are two things to know about xanthine oxidase inhibitors. First is that they can **precipitate a gouty flare** when initiated. Second is that they should **not be discontinued** because of a gouty flare. A patient with hyperuricemia has high levels of uric acid. Before treatment with a xanthine oxidase inhibitor, they are also in equilibrium. The amount being made, excreted, and crystallized out is in balance. When a xanthine oxidase inhibitor is started, less uric acid is made. The excretion rate remains unchanged, so the plasma uric acid levels fall. All of this we want to happen. But now the equilibrium between the blood and joints favors the uric acid's leaving the joints back into the blood. That sounds even better! But this **mobilization** of uric acid from all joints **can precipitate crystallization** in just one joint. **Continue** the xanthine oxidase inhibitor and treat the acute flare. Because initiation of xanthine oxidase inhibitors is known to provoke an acute flare, and because colchicine is most effective in the first 24 hours, give that patient a "pill-in-the-pocket" (an on-demand colchicine) to be given if symptoms start.

A low-yield thing to get that extra point is that levels of azathioprine and 6-mercaptopurine (which are purine analogs and metabolized by xanthine oxidase) will increase if given with a xanthine oxidase inhibitor, and may lead to systemic toxic effects. If you see xanthine oxidase and a drug interaction question, don't go for P450 interactions; pick an answer related to purine metabolism.

Pathogenesis and Management of Urate Underexcretion

Uric acid is filtered by the glomerulus and then both secreted and absorbed by the tubules of the nephron. It is the way uric acid is eliminated—renal clearance. Without adding diet or medications to the mix, any one individual's uric acid elimination is generally fixed—some people happen to have less of it than others. Patients with hyperuricemia are generally underexcreters. That does not change the fact that xanthine oxidase inhibitors are the preferred initial management.

A few things can change a patient's baseline excretion. We explore the risk factors, broken down into the three phases of elimination—filtration at the glomerulus, resorption by the tubule, and finally secretion by the tubules. We then use this information to overlay the pharmacology of uricosuric agents and uricase agents.

Filtration. The only way to alter filtration of uric acid is to change the glomerular filtration rate (GFR). The lower the GFR, the less uric acid gets filtered. A low GFR means **chronic kidney disease** (CKD). A low GFR from acute kidney injury does not seem to provoke flares. As a patient's CKD progresses, they become at increased risk for hyperuricemia and gout attacks. All CKD is treated regardless of uric acid levels. The only problem is that we manage CKD complications, and attempt to prevent further decline of GFR. We cannot reverse CKD. Which means CKD is a **nonmodifiable risk factor** for hyperuricemia and gout.

Resorption. There are no nonpharmacologic treatments that affect reabsorption of uric acid from the tubules. We'll talk probenecid in a few paragraphs. Probenecid does target resorption.

Secretion. There are several considerations for secretion of uric acid. **Alcohol metabolites** compete with uric acid for uric acid secretion channels. Acute alcohol consumption tips the balance against uric acid secretion, acutely raising the serum levels of uric acid, precipitating a flare. **Diuretics** (loops and thiazides) also reduce uric acid secretion. If a patient has hyperuricemia and a comorbid condition that is treated with diuretics, see whether there are other options. Finally, **low-dose salicylates** can reduce secretion of uric acid. Patients on a low-dose aspirin for coronary artery disease may need to be switched to another antiplatelet.

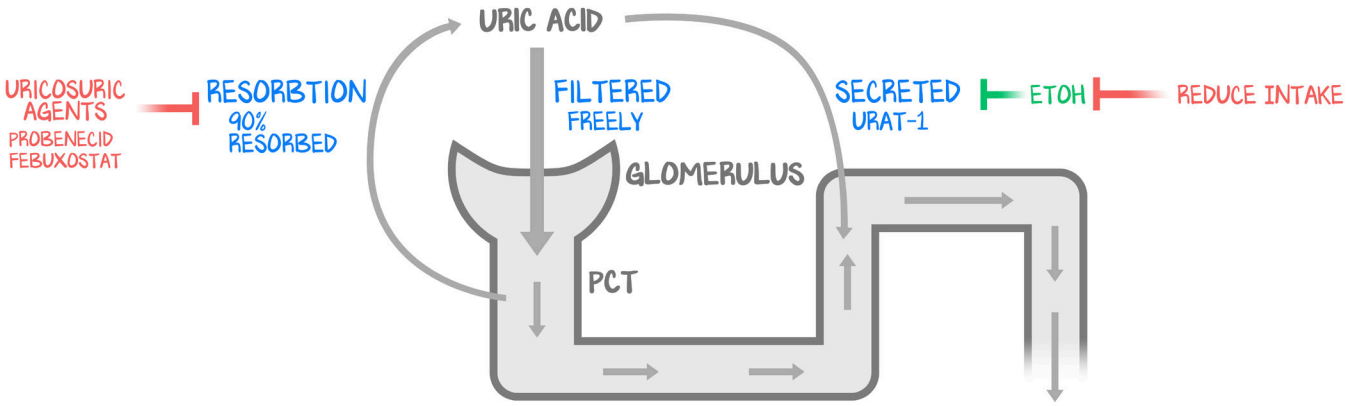

Figure 2.4: Lowering Uric Acid by Targeting Elimination
Alcohol, diuretics, and low-dose salicylates (aspirin) inhibit tubular secretion of uric acid, causing uric acid levels to rise. This both chronically increases the chances for flares and (especially alcohol) can precipitate a flare when ingested. Avoiding alcohol intake can help prevent flares. Uricosuric agents (such as probenecid) inhibit tubular resorption of uric acid, decreasing plasma uric acid levels by facilitating elimination in urine.

Uricosuric agents. Pharmacologically, we manipulate **tubular resorption** with the medication **probenecid**, which prevents reabsorption of uric acid in the **proximal convoluted tubule**. Probenecid also inhibits penicillin secretion and can cause supratherapeutic doses of β-lactams. Probenecid is known as a **uricosuric agent** because it causes uric acid to be excreted in the urine. If there is more uric acid in the urine, it makes the formation of **uric acid stones** more likely, so avoid in patients who have uric acid nephrolithiasis. It is also a **sulfa drug** (like TMP/SMX), and is notorious for causing sulfa drug reactions and skin eruptions. Finally, it requires good renal function to work—filtration must occur first in order to prevent resorption—and a major risk factor for hyperuricemia is CKD. Given the complications of uric acid stones, sulfa drug reactions, and a weakened efficacy in CKD, probenecid is therefore usually given as a second agent when other urate-lowering therapies have failed to achieve target uric acid levels.

Uricase agents. The enzyme **uricase** is an enzyme that humans do not produce (pigs do). Uricase converts uric acid into allantoin, a more water-soluble compound than uric acid. This has two benefits: it eliminates uric acid through biotransformation (allantoin doesn't form uric acid stones, nor does it form urate monosodium crystals), and allantoin is more water soluble than uric acid, so is more easily excreted. There are two uricase agents—pegloticase and rasburicase. Both are recombinant pig enzymes, and, being foreign proteins, can cause immune reactions. **Pegloticase** is pegylated (lasts a long time and has reduced immunogenicity) and is given intravenously every two weeks. It is used only in **treatment-refractory gout**, after xanthine oxidase inhibitors and probenecid have failed. **Rasburicase** is another uricase agent that is NOT pegylated, so has a rapid on and rapid off effect. It is used specifically when treating tumor lysis syndrome where the destruction of leukemic cells is provoking renal failure. This example, this one unique case, is where acutely reducing uric acid levels in an acute attack is indicated.

TREATING FLARES	URATE-LOWERING STRATEGIES	PROPHYLAXIS
Colchicine if within 24 hours	Xanthine oxidase inhibitors (allopurinol or febuxostat)	Colchicine (danger pharma)
Fast-acting NSAIDs (ibuprofen) if established flare	Uricosuric agents (probenecid, XO-i failure)	Long-acting NSAIDs (naproxen)
Glucocorticoids (intra-articular, fewer side effects than oral)	Uricase agents (pegloticase, last line)	No glucocorticoids for long periods

Table 2.2: Clinical Management of Gout

DRUG	MECHANISM	INDICATION	SIDE EFFECT
Colchicine	Microtubule polymerization inhibition, neutrophil chemotaxis and degranulation	Gout flare < 24-hr dur Gout flare prophylaxis	Diarrhea
NSAIDs	Anti-inflammatory	Gout flare > 24-hr dur Gout flare prophylaxis	Gastritis AKI (cannot use in CKD)
Intra-articular glucocorticoids	Anti-inflammatory	Alternate to NSAIDs for acute flare	Less than systemic
Oral burst glucocorticoids	Anti-inflammatory	Alternate to NSAIDs for acute flare	HTN, hyperglycemia, confusion

Table 2.3: Medications for Acute Gout

DRUG	MECHANISM	INDICATION	SIDE EFFECT
Allopurinol	Xanthine oxidase inhibitor	First-line urate-lowering agent	Can precipitate flare (do not discontinue)
Febuxostat	"Allopurinol"	"Allopurinol"	"Allopurinol"
Probenecid	Blocks proximal tubular reabsorption of urate	Xanthine oxidase augmentation if no CKD	Sulfa allergies Uric acid stones
Pegloticase	Recombinant uricase, metabolizes urate into allantoin	Treatment of refractory tophaceous gout	N/A
Rasburicase	Recombinant uricase	Tumor lysis	N/A

Table 2.4: Medications for Hyperuricemia